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The value of treating the sexual partners of women with recurrent vaginal candidiasis with ketoconazole

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Abstract

***Objective*—To determine whether treatment of the sexual partners of women with chronic vulvovaginal candidiasis with oral ketoconazole can reduce the recurrence rate of candida vaginitis.**

***Design*—Single blind randomised study where all the women were treated with ketoconazole 400 mg daily for 7 days after an acute episode of candida vaginitis and half the male partners were treated with ketoconazole 200 mg daily for 5 days.**

***Setting*—Women's Candida Clinic of St. Michael's Hospital, a University of Toronto teaching Hospital, Toronto, Ontario, Canada.**

***Subjects*—Fifty-four women attending the clinic with at least four proven episodes of candida vaginitis and their male sex partners (stable monogamous relationships) were enrolled in the study.**

***Main Outcome Measures*—Clinical recurrence of candida vaginitis with confirmation by smear and culture. Follow-up was obtained one to two weeks after initial treatment, then monthly for one year.**

***Results* —In the control group (untreated partners), 20 of 28 (71%) patients had recurrences in six months, versus 17 of 26 (65%) patients in the treated group (treated partners) (95% Confidence Interval (CI) for the difference in recurrence rate = −19% to 31%). At one year, 23 of 28 (82%) patients in the control group had recurrences, versus 22 of 26 (85%) in the treated group (CI = −23% to 17%).**

***Conclusion* —Treatment of the male partners, with a brief course of ketoconazole, is not of value in reducing the incidence of relapse in women with recurrent vaginal candidiasis. It is unlikely that a larger study would show a clinical important difference.**

Introduction

Most women will experience at least one episode of genital candidiasis in their lifetime.[1] However, these episodes occur infrequently and are easily treated. Various factors have been cited as predisposing to vulvovaginal candidiasis, among them: prolonged or recurrent use of antibiotics[2] or steroids,[3] diabetes mellitus;[2] pregnancy;[4] and immunodeficiency.[5] There exists a sub-group of women with recurrent or refractory genital candidiasis who are otherwise healthy and have none of these risk factors.[6] The aetiology of their recurrent infections is unknown, although a few preliminary studies suggest that some of these women may have a selective defect in their cellular immunity.[7 8] Perhaps the most widely held hypothesis on recurrent infection is that of persistent intestinal carriage of the yeast pathogen.[9-11] Reinfection from the sexual partner has also been considered important.[12-14] Treating the sexual partner to eradicate penile carriage is frequently done, but no published controlled studies have proven the efficacy of this approach.

The aim of this study was to determine the value of treating the male partners with ketoconazole, in preventing recurrence of vaginal candidiasis. Our objective was to detect a 50% reduction in the relapse rate in six months to one year.

Methods

This study was approved by the Clinical Trials Committee of St. Michael's Hospital and written informed consent was obtained from all patients prior to enrolment. Patients with diabetes mellitus, chronic antibiotic or steroid use and chronic illnesses were excluded.

Fifty-eight women from our Candida Clinic and their sex partners were selected for study. Only couples with stable monogamous relationships were enrolled in the study. The women had ⩾ four episodes of candidiasis (proven by culture) in the year preceding the study. Demographic information was obtained for all patients admitted to the study.

Treatment of partners was single-blind and randomised. Partners received either 200 mg ketoconazole daily for five days or no treatment. Numbered envelopes contained the specific regimens. All women received 400 mg ketoconazole daily for seven days at the time of diagnosis of acute candida vaginitis. Vaginal washings and swabs from the vulva and vagina were cultured for yeast on Sabouraud's and blood agar, containing antibiotics to suppress normal bacterial flora. Identification of yeasts was done by the germ tube method using human serum, production of chlamydospores on Tween 80 and sugar assimilation when necessary. Initial genital swabs were cultures for *Neisseria gonorrhoea, Gardnerella vaginalis, Chlamydia trachomatis,* and *Trichomonas vaginalis.*

Moistened swabs were taken of the glans penis/sulcus and anterior urethra of male sex partners for *Candida albicans.* Samples from partners of infected women were cultured

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before therapy; after therapy, at intervals which varied according to patient compliance; and at relapse of the female. Patient assessments and cultures were done one to two weeks after treatment, then monthly for one year and when symptomatic recurrences occurred. Recurrence of candidiasis was considered definite if cultures were positive for *C. albicans* and associated with symptoms or signs of candidiasis. Patients with confirmed recurrence of candida vaginitis were treated with clotrimazole vaginal ovules but the partners were not re-treated.

Student's *t* test was used to compare the mean patient age for each treatment group; the mean number of candidiasis episodes per year; the mean frequency of intercourse in each group; and the mean number of cultures done for male partners.

Post-treatment infection rates in the patients and rate of oral contraceptive use in each group were analysed by the χ square test with Yates's correction, as were all recurrence rates except those at 12 months. Recurrence rates at 12 months and pre-treatment colonisation rates in male partners were analysed using Fisher's exact probability test (2 tailed). Ninety-five percent confidence intervals (CI) were calculated for all results expressed as rates.[15]

Results

The demographic features of the two groups (table 1), were comparable. Of the fifty-eight patients admitted to the study and treated, fifty-four were evaluable. In group 1 (treated partners), two patients dropped out of the study, owing to lack of interest; in group 2 (untreated partners), one patient was removed from the study, after one day treatment, because of a severe adverse reaction to the treatment drug, and one dropped out from disinterest. Sixteen (28%) of the women treated had an adverse reaction to the drug, which was most commonly mild nausea (11/16 or 69%). The one severe reaction involved flushing, dizziness and slight blurring of vision associated with weakness. Light headedness and diarrhoea accounted for the remaining reactions.

The initial (pre-treatment) candida colonisation rate for male partners was, for the two groups combined, 7/45 (16%). Individual rates were: 4/23 (17%) for group 1 (CI = 7% to 36%); and 3/22 (14%) for group 2 (CI = 5% to 34%). Post treatment, the penile colonisation with *C. albicans* was found to be transient and intermittent with some swabs being positive and others negative for yeast in the same patients without further therapy.

Intermittent colonisation rates in the male partners over six months, with *C. albicans* were 12/26 (46%) in group 1 (CI = 29% to 65%); and 8/26 (31%) in group 2 (CI = 17% to 50%), p = 0·29.

At the end of treatment assessment all patients had resolution of their symptoms, signs and mycological evidence of acute candida vaginitis. At one month, 8/26 (31%) of women in group 1 versus 9/28 (32%) of women in group 2 had recurrence (CI = 17% to 50% and 18% to 51%, respectively, (table 2)). By three months post-treatment, most patients had recurrences: 17/26 (65%) in group 1 (CI = 46% to 80%); 17/28 (61%) in group 2 (CI = 43% to 77%). At six months the rate of recurrence in group 1 remained unchanged; in group 2 there were now 20/28 (71%) recurrences (CI = 52% to 83%). Lastly, at twelve months, the cumulative recurrence rates (fig) were 22/26 (85%) in group 1 (CI = 66% to 94%); and 23/28(82%) in group 2 (CI = 64% to 92%). At no time was the difference in recurrence rates between the two groups statistically significant.

Table 1 Demographic data for study subjects with recurrent vaginal candidiasis

	*Group 1**	*Group 2†*	*p. value*
No.of Patients	26	28	—
Mean Age (years), SD‡	32·0, 7·0	31·1, 5·4	0·06
Range (years)	23–49	19–41	—
Rate of Oral Contraceptive Use (%)	6 (23)	9 (32)	0·66
Post-Menopausal	1	0	—
Mean no. of candidiasis episodes per year, SD	8·4, 3·36	9·5, 3·28	0·50
Mean frequency of intercourse (times per week), SD	2·6, 1·4	2·0, 1·7	0·20

*Group 1 = Treated partners
†Group 2 = Untreated partners
‡Standard deviation.

Table 2 Relapse after treatment

	*Group 1** *n = 26*	*Group 2** *n = 28*	*95% CI†*	*p value*
1 month (%)	8 (31)	9 (32)	−24% to 26%	0·85
3 months	17 (65)	17 (61)	−30% to 22%	0·94
6 months	17 (65)	20 (71)	−19% to 31%	0·85
12 months	22 (85)	23 (82)	−23% to 17%	0·55

*Group 1 = Partners treated; Group 2 = Partners untreated
†95% confidence interval for the difference in relapse rates between groups.

Discussion

Few published studies have investigated the value of treating the male partner of women with recurrent vaginal candidiasis. The results of this study suggest that treatment of the male partner does not effectively reduce the incidence of relapse in women who suffer from chronic candidal infection. Hence, the male partner does not appear to play a role in recurrent vulvovaginal candidiasis. Further most patients have recurrence within three-months after treatment with ketoconazole.

This study was designed to detect a 50% difference in relapse rates between the two groups. It is possible that with a larger number of subjects, a small difference in recurrence rates might have been detected. However, I feel that for a potentially minimal difference, routine prophylactic treatment of the male partner would not be worthwhile.

A study by Sobel[16] of women with severe recurrent vulvo-vaginal candidiasis included examining the effect of treating male sexual partners with topical miconazole genital therapy. The treated group had a significantly lower clinical recurrence of symptomatic candida vaginitis during the first six months of follow-up, but late recurrences at one year were not altered. The results of my study were some-

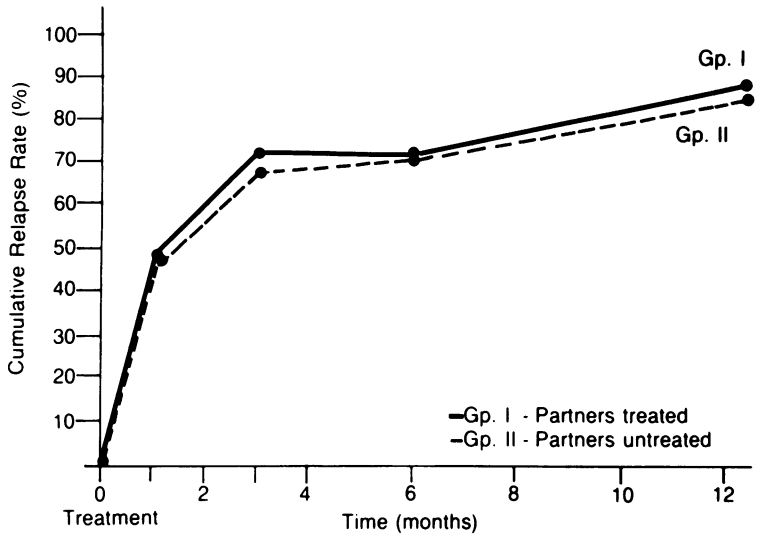

Fig The cumulative relapse rates of vulvo-vaginal moniliasis after treatment are shown for the two groups

what different in that no differences were found in recurrent candidiasis at any time, including at six months follow-up. Buch and Christensen[17] treated male partners of women with vaginal candidiasis with natamycin cream or placebo. They found that the recurrence rate was the same whether or not the male partner was treated. Both of the aforementioned studies of topical genital therapy showed that reinfection from the partner's genitalia was unlikely, but could not rule out infection from the partner's urethra or gastrointestinal (GI) tract. Recently, Ogunbanjo[18] reported that 14 of 20 husbands of women with recurrent vaginal moniliasis grew *Candida spp.* from their seminal fluid. This raised the issue of sexual transmission that would not be prevented by topical therapy. Ketoconazole was selected for this trial because of its systemic antifungal effect and wide tissue penetration. Thus, ketoconazole would likely be more effective than topical therapy in preventing sexual transmission of yeast.

In another study addressing the issue of sexual transmission of candida, Horowitz *et al*[19] studied 33 couples. Colonisation of men with yeasts were found in the oral cavities of 36%, the rectum in 33% and the ejaculate in 15%. Prostatic cultures were all negative. Elimination of the yeast in each site using clotrimazole oral troches, nystatin oral tablets or ketoconazole resulted in cures of the women. Five men with positive ejaculate culture received ketoconazole 200 mg daily for 14 days. However, since this was an uncontrolled, non-randomised study, the results are inconclusive. In our study, the ejaculate or seminal fluid was not obtained for cultures, and although the dosage of ketoconazole used was the same, the duration of treatment was shorter.

In conclusion, treatment of the sexual partners of women with recurrent vulvovaginal candidiasis with a brief course of ketoconazole was ineffective in reducing recurrences. This suggests that sexual transmission of candida is not a major factor in recurrent vulvovaginal candidiasis.

This study does not exclude the possibility that in a small subgroup of couples, sexual transmission by ejaculate or seminal fluid may play a role in perpetuating recurrent candidiasis. Future research in this area should be directed at couples with positive yeast cultures from ejaculate or seminal fluid, and should be randomised controlled studies with a systemic antifungal agent such as ketoconazole or fluconazole used for at least two weeks in duration.

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